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Hereditary angioedema – as Recurrent Allergic Manifestation

Amar verma[1], Neelotpal[2], Md. Monazeer Ahsan[2], Rani Manisha[2*]

[1]Professor, Department of Paediatrics & Neonatology, Rajendra Institute of Medical Sciences, Ranchi, India
[2]Junior Resident (Academic), Rajendra Institute of Medical Sciences, Ranchi, India

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ABSTRACT

Background

A 13 years old female child presented with complains of breathing difficulty with concurrent swelling of whole face and neck region. This presentation was preceded by mild trauma over lips only one day back. The injury was quite innocuous in nature. There was history of similar episodes in family. Family pedigree chart shows similar episodes in grandfather, uncle and two sisters of her father. She is only one affected out of four sisters in her family. Her father died with same problem 12 years back.
Her C1-INH was assessed quantitatively and functionally. Her C1 esterase inhibitor (C1-INH) level is normal in quantification assay but significantly below normal functionally. The case was diagnosed as a case of Hereditary angioedema disguising as recurrent allergic manifestations leading to anaphylactic reaction like feature. This condition does not respond to classical antihistaminics or steroids. This presentation further highlights significance of consideration of above mentioned condition in patient reporting for repeated allergic and anaphylactic reactions.

Keywords: hereditary angioedema, laryngeal edema, minor trauma, anaphylaxis.

Introduction

Hereditary angioedema (HAE) is an autosomal dominant disease caused by low functional levels of the plasma protein C1-INH[1,2].Patients typically report episodic attacks of angioedema or deep localized swelling, most commonly on a hand or foot, which begins during childhood and becomes much more severe during adolescene[3]. Cutaneous non-pitting and non-pruritic edema is associated with urticaria presents as commonest symptom. The swelling becomes more severe over about 1.5 days and those resolves over about same period.

In some patients attack are preceded by the development of rash, which is erythema marginatum & is associated with erythematous lesion which not raised non pruritic.

The second major symptom complex noted by patients is attack of severe abdominal pain caused by edema of the mucosa of any portion of gastro-intestinal tract. It may lead to life threatening complication of laryngeal edema [4].

**Correspondence*
Dr. Rani Manisha
Junior Resident (Academic), Rajendra Institute of Medical Sciences , Ranchi, India
E Mail: rnmnsh@gmail.com

There is depression of complements C_4 and C_2 during an attack significantly reducing the CH_{5c}. Typically, C_4 is low and C_3 normal or slightly decreased [5,6]

HAE is classified into three types of dysfunction:

1. Type 1 HAE is caused by decreased production or absence of C1 esterase inhibitor (C1-INH)[5,6]
2. Type 2 HAE is characterized by normal C1-INH level indicating functional impairment [7].
3. Type 3 HAE has been described in female only and presents normal function C1-INH levels [8].

Case description

13 years old female child was brought to hospital with complain of breathing difficulty and swelling of whole face and neck followed by mild trauma over lips. Past history includes similar episodes (6-7 times) occurred in past. Last episode occurred about 4 months ago. History of minor trauma such as trauma while brushing her teeth, playing etc was always presents preceding an attack of angioedema. Earlier she used to take Tab Avil and Dexona for relief but this was first time she was hospitalized.

Family history of similar episodes in her grandfather then her father, one uncle and two of her father's sister is present. She is only one affected among her siblings.

12 years back her father died with same problem. He was never hospitalized nor investigated.

After admission she was advised Inj Avil, Hydrocortisone, Nebulisation with levolin, moist o_2 inhalation, monitoring of vitals. Within 12 hours she recovered. She was investigated for CBC,RFT,LFT, serum electrolyte, IgE levels, absolute eosinophil count, serum tryptase level, serum C1-INH level and function. In these CBC, RFT, LFT, serum electrolyte were normal.

Her C1 Esterase Inhibitor - Quantification (C1 Inactivator – Quantitative)(Radial Immuno diffusion) was 95 mg/L (normal)

Her C1 Esterase Inhibitor - Functional (C1 Inactivator - Functional) was 4 % (below 40 % is considered abnormal), thus confirming the diagnosis.

Fig 1: A 13-year-old girl exhibiting diffuse facial swelling involving forehead and both the eyes

Fig 2: Recovery of the 13-year-old girl after 5 days

Discussion

There are many known HAE episode inciting factors, including physical injury, medical or dental operations, psychological stress, menstruation, infections or certain medications – a list that includes contraceptive pills and angiotensin-converting enzyme (ACE) inhibitors. During the acute phase of an HAE episode manifestations may include diffused skin, peptic and respiratory mucosa oedema. Cerebral oedema may also occur, leading to migraine type pain, as well as cerebrovascular incidents . Face oedema may be limited to the eyelids only or may extended to its entire surface, the lips and, rarely, to the oral cavity (tongue and soft palate)[7]. The combination of lip swelling in the form of *cheilitis glandularis* and face swelling, which constitute the characteristic clinical findings of Melkersson–Rosenthal syndrome can, during the first stages of its appearance, lead to the mistaken diagnosis of angioedema. A tip for helping differentiate the two is that in the case of *cheilitis glandularis* lip swelling is stable and it is not accompanied by other findings that lead to the diagnosis of angioedema.

Gastrointestinal system symptoms are caused by visceral oedema, which include anorexia, nausea/or vomiting and abdominal pain. Fluid extravasations into the peritoneal cavity as a result of vasodilatation in HAE may sometimes lead to ascites and fluid imbalance that can lead to hemodynamic shock, which

requires aggressive fluid resuscitation to prevent this potentially severe complication[3]

A common presentation of an HAE episode concentrated in the gastrointestinal tract is severe abdominal pain accompanied by nausea or vomiting and is often indistinguishable from an acute abdomen. This can lead to misdiagnosis and unnecessary surgical operations, of which appendectomy is the most common. Gastrointestinal tract attacks usually subside within 12 - 24 hours[3]

Findings similar to those seen in HAE can be observed in patients prescribed ACE inhibitors for hypertension or/and congestive heart failure treatment. The incidence of angioedema in patients taking ACE inhibitors is approximately 0.1% to 0.5%. Distinguishing between HAE and angioedema induced by ACE inhibitors is achieved by reviewing the patient's medical history and their C1-INH levels: Those with ACE-induced angioedema will relate no prior episodes of angioedema, will note that their angioedema did not develop until they were treated with ACE, C1-INH levels will be normal in this situation.

For patients who develop ACE-induced angioedema the issue should resolve with discontinuation of the ACE. The physician then provides the patient an alternative therapy instead of an ACE for the condition being treated[7].

HAE usually presents during the second decade of life but may also appear at other ages. Bork et al, having studied 123 cases of HAE patients, came to the conclusion that first HAE appearance was most frequently seen between 11 to 45 years of age, while the youngest known confirmed case at that time was 3 years old.

The intervals between HAE crises differ between patients and may also differ in the same patient. Factors that influence frequency of HAE episodes among others depend on motivating factors existence and whether the patient is being prescribed long-term medication prophylaxis.

As stated previously, oedema can affect many body regions but laryngeal oedema constitutes the most worrisome potential symptom of HAE, as it can cause death by asphyxiation. Life-threatening laryngeal oedema can be an HAE patient's initial presenting HAE symptom, it might follow face or extremity oedema, or it could appear during every episode in a specific HAE patient.

Bork and Barnstedt report four fatal laryngeal oedema cases in HAE patients where oedema appeared 4 to 30 hours following tooth extraction. The patients' medical history examination revealed that 3 out of these 4 patients had developed laryngeal oedema for the first time. C1-INH was not administered to any of them either prophylactically or therapeutically a factor that may have contributed to their poor clinical outcomes.

Bork et al., after studying 123 HAE patients, concluded that roughly half of them (61 patients – 49, 6%) had experienced one or more laryngeal oedema episodes. When they compared the incidences of laryngeal oedema to skin oedema to oedema of internal organs, the oedema rate was found to be laryngeal : skin : internal organs = 1 : 70 : 54. They thus concluded that upper airway system attack (larynx) is less common (1 laryngeal oedema in 125 angioedema episodes). They further noted that the interval between the initial appearance of laryngeal oedema and its complete appearance ranged from 8 to 12 hours, with the mean time being 8.3 hours (only one patient had laryngeal oedema that appeared in less than 3 hours) .

According to the above researchers, factors that increase likelihood of laryngeal oedema in HAE are:

• Preceding dental operation or general anaesthesia (intubation);
• Age between 11 - 45 years;
• Prior, or multiple, laryngeal oedema episodes;
• Prior episode of face oedema (face oedema does not always precede laryngeal oedema).

They also described the following factors that reduce the likelihood of laryngeal oedema in HAE:

• Age under 11 years and over 45 years;
• Absence of prior laryngeal oedema episode (one must still keep in mind that even first episode of laryngeal involvement could be fatal episode;
• Long-term medical prophylactic therapy.

The management of HAE is multifactorial and consists of long-term maintenance/prophylaxis a factor that includes avoidance of situations or activities known to incite episodes in the specific patient, prophylaxis prior to dental or medical procedures(short-term prophylaxis) and, finally, medical management of acute angioedema episodes (acute phase) . If one excludes C1-INH, angioedema prevention measures include attenuated androgen administration (danazol-stanozolol), fresh frozen plasma (FFP), and antifibrogenolytic factors such as E-aminocaproic acid and tranexamic acid. Corticosteroids and antihistamines administration is not helpful in HAE patients. C1-INH provided before medical and dental procedures is effective in the prevention of angioedema as well as in the management of acute HAE episodes, including laryngeal oedema. Alternatively, preoperative administration of FFP is recommended, especially in those countries where C1-INH is not

available. However, FFP administration has two disadvantages:

1. Possible transmission of contagious disease, including hepatitis B, C and HIV infection, amongst others, because it is a biological product
2. Aanaphylactic shock or resurgence of angioedema due to the fact that FFP consists of supplement factors, including C4.

Accordingly, FFP administration is not recommended in acute angioedema episodes because C4 excess caused by FFP can intensify existing oedema. For these reasons Turner et al. suggest administration of recombinant plasma kallikrein inhibitor (OX-88) use prior to dental operation in the hopes of preventing bradykinin formation, a factor responsible for angioedema appearance.

Conversely, some authors underline the necessity of further clinical studies for evaluating the safety and effectiveness of this factor in both the prophylaxis and acute management of HAE patients.

Factors that combat fibrinogenolysis, including E-aminocaprioc acid and tranexamic acid, are used in long-term HAE prophylaxis. These factors impede C1 and plasmin activation. Attenuated androgens (danazol-stanozolol) are the most frequently used prophylactic regimen in the management of HAE. Androgens are clinically proven to reduce oedema occurrence in skin and internal organs as well as abdominal pain. They also reduce both the frequency and severity of laryngeal oedema episodes. Nevertheless, their use is limited due to their numerous and significant side effects, including weight gain, headache, myalgia, hypertension, libido decrease and liver concerns, including hepatic adenomas and hepatic carcinoma. Additionally, side effect concerns specific to female include menstrual disturbances and masculinization (muscle hypertrophy, breast reduction, and deepening of voice). The presence of these possible side effects has resulted in the need for minimal dosing in these populations and the recommendation that children and young women be excluded from using attenuated androgens as a prophylactic regimen in their HAE management strategy.

Administration of C1-INH factor is effective in both dental and medical procedural prophylaxis and treatment of acute HAE episodes, including laryngeal oedema. Studies have revealed that failure to administrate C1-INH on laryngeal oedema was fatal to patients. Also, because HAE is not an allergic condition, corticosteroid and antihistamines administration does not constitute an effective therapy. Awareness among doctors, paramedicals, and general public is essential as it is not an allergic condition and doesnot responds to usual antihistaminics and corticosteroids.

Screening of condition among relatives of confirmed cases is essential.

Finally, the importance of educating patients and their relatives about the disease and its potentially severe complications, including acute laryngeal oedema, cannot be stressed highly enough. Patients must truly understand that the best way to prevent possibly avoidable loss of life from laryngeal oedema is early recognition followed by presentation of the patient for emergency care.

Conclusion

Prevention and early recognition of potential laryngeal oedema that can occur as a complication of minor trauma may be lifesaving for HAE patients.

Reference

1. Khan DA. Hereditary Angioedema: Historical aspects, classification, pathophysiology, clinical presentation and laboratory diagnosis. *Allergy Asthma Proc*. 2011; 32(1): 1-10
2. Frank MM , Gelgand JA, Atkinson JP. Hereditary Angioedema: the clinical syndrome and its management. *Ann Inter Med* 1976; 84: 589-93
3. Pearson KD, Buchignani JS, Shimkin PM, Frank MM . Hereditary angioneurotic edema of the gastrointestinal tract. Am J Roentgenol Radium Ther Nucl Med. 1972; 116: 256-261.
4. Bork K, Barnstedt SE. Laryngeal edema and death from asphyxiation after tooth extraction in four patients with hereditary angioedema. J Am Dent Assoc. 2003;134(8):1088-94.
5. Hereditary Angioedema: the clinical syndrome and its management. Ann Inter Med 1976; 84: 589-93.
6. Zuraw BL. Clinical Practice. Hereditary Angioedema: the clinical syndrome and its management. N Engl J Med 2008; 359(10): 1027-36.
7. Nzeako UC, Frigas E, Tremaine WJ. Hereditary angioedema: a broad review for clinicians. Arch Intern Med. 2001;161(20):2417-29.

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